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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,009	08/06/2002	Carolyn K. Goldman	NIH-05111	5287

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EXAMINER	
JIANG, DONG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,009	GOLDMAN ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,9,11-15 and 22-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,9,11-15 and 22-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's amendment filed on 21 Match 2006 is acknowledged and entered. Following the amendment, claim 4 is canceled, claims 1, 3, 5, 9, 24 and 25 are amended, and the new claims 26-29 are added.

Currently, claims 1, 3, 5, 9, 11-15 and 22-29 are pending and under consideration.

Withdrawal of Objections and Rejections:

All objections and rejections of claim 4 are moot as the applicant has canceled the claim.

The rejection of claims 1, 3-5, 9, 11-15 and 22-25 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of applicant's amendment.

Declaration

The second declaration by Dr. Waldmann under 37 CFR 1.132 filed on 21 Match 2006 is insufficient to overcome the prior art rejection of claims 1, 3, 5, 9, 13-15, 22 and 23 based upon Colamonici et al. (J. Immunol., 1990, 145:155-160) under 35 U.S.C. 102(b), or, in the alternative, under 35 U.S.C. 103(a) as set forth in the last Office action for the reasons below, which will be addressed according to the following:

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things (*Ex parte Simpson*, 61 USPQ2d 1009 (BPAI 2001)):

1) the nature of the fact sought to be established,

2) the strength of any opposing evidence,

3) the interest of the expert in the outcome of the case (For example, the fact that affiant is not independent of the inventor or the assignee is relevant to the weight to be given to the affidavit. *Cf. Redac Int'l. Ltd. v. Lotus Development Corp.*, 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996); *Paragon Podiatry Lab., Inc. v. KLM Lab., Inc.*, 948 F.2d 1182, 1191, 25 USPQ2d 1561, 1568 (Fed. Cir. 1993),

4) the presence or absence of factual support for the expert's opinion (unless an "expert" states the underlying basis for an opinion, it may be difficult to accord the opinion significant weight in overcoming the rejection).

The declaration indicates, besides those presented in the first declaration filed on 17 June 2005, that experimental results (Exhibit 1) demonstrate that ILRAPs in MT-1 cells immunoprecipitate with 5F7 mAb are different in molecular weight from that immunoprecipitated with anti-Tac antibody (used by Colamonici) as they do not migrate in an equivalent fashion when run side by side on SDS-PAGE, and thus, they cannot be the same peptide (item 6). This has been fully considered, but is not deemed persuasive because of the following: first, the rejection is based on Colamonici's teachings of Hut 102 cells, not MT-1 cells as the presently claimed polypeptides are from Hut 102 or Kit-225 cells. Although Colamonici teaches that the 37 and 20 kDa bands also appeared in MT-1 cells, it is unclear if they are the same molecules as that in Hut 102 cells, which are also disclosed by Colamonici. Thus, there is no direct factual evidence being established. Merely same MW does not automatically indicate that they are the same molecules, especially given the fact they are from different cell sources. As opposing evidence, Colamonici teaches, for example, that ICAM-1 protein is closely associated to IL-2R, and has a MW of 95 kDa, which is very similar to that of the γ-subunit of IL-2R (95-110 kDa), but they are distinct molecules (page 158, the paragraph bridging the two columns), even though they have similar MW and association to IL-2R. Second, applicants interpretation of the experimental results (Exhibit 1) is not convincing because the lower band shown in lane 3 (anti-Tac Ab) is comparable to that of 5F7 protein in lane 2 in MW, i.e., the MW of the lower band in lane 3 is well within the range of that of "5F7 protein" in lane 2. Given the broad band in lane 2, there is no basis for concluting that the band in lane 3 is not the same protein.

Item 7 of the declaration indicates that an SDS-PAGE analysis (Exhibit 2) shows the MW of 5F7 polypeptides are between 31-36 kDa and 22-30 kDa, respecitvely, which sizes are different from those of Colamonici's (37 and 22 kDa, respecitvely). This has been fully considered, but is not persuasive because the bands shown in lanes 2 and 3 are extremely broad (>1cm), indicating overloading/overexposing, and the upper boundary of the 31-36 kDa band in lanes 2 and 3 passed the lower edge of the 45 kDa band in lane 5 (MW marker). As such, it is

impossible to determine MW of the indicated bands with acuracy from such a result, especially within the range of 1 kDa, and once again, there is no factual evidence being established for the purpose of distinguishing said polypeptides.

In item 8 of the declaration (similar to item 6 of the previous declaration), applicants repeatedly argue that the claimed 5F7 polypeptides remain present after Kit225 cell lysate was pre-cleared with anti-Tac antibody, leading to the conclusion that the anti-Tac antibody of Colamonici does not recognize the polypeptides identified by anti-5F7 antibody as evidenced by anti-Tac's inability to precipitate the claimed polypeptides from the lysate after the Tac protein was eliminated. This has been fully considered, but is not persuasive because of the following. First, Colamonici merely teaches that anti-Tac antibody is a monoclonal antibody for IL-2Rα, recognizing the IL-2 binding site on p55 (IL-2Rα), and the reference never teaches that anti-Tac antibody also recognizes the 37 and 22 kDa polypeptides or any other molecule. Therefore, applicants argument that anti-Tac antibody does not recognize the present polypeptides is irrelevant. The presence of those bands can be the result of co-precipitation with IL-2Rs in the presence of IL-2 by the anti-Tac antibody since Colamonici's cells or lysate was crosslinked with IL-2. With respect to the inability of the anti-Tac mAb to remove the claimed ILRAPs from Kit225 cell lysate where both Tac (IL-2Rα) and the claimed polypeptides are expressed, whereas Colamonici's lower MW polypeptides were present in cells when crosslinked with IL-2 and precipitated with anti-Tac antibody, there is no evidence in the Colamonici's reference shows that IL-2Rα is directly associated with the 37 and 22 kDa polypeptides as anti-IL-2 antibody was also able to co-precipate the polypeptides. Further, the 37 kDa polypeptide is also detected by anti-IL-2 antibody 17A1 in MLA-144 lacking IL-2Rα (Figure 4B), which suggests that IL-2Rα may not directly associate with those polypeptides. Therefore, it would depend upon the experimental conditions (which are not detailed in the present declaration), unless IL-2Rs (including IL-2Rα) and associated molecules are under condtions to form complex (in the presence of IL-2, for example), anti-Tac antibody would not be able to "pre-clear" said low MW polypeptides.

It is noted that the results in lane 2 (anti-5F7 antibody from non-pre-cleared Kit225 cell lysate) and lane 8 (anti-5F7 antibody from anti-Tac pre-cleared Kit225 cell lysate) appear the

same. Based on such results only, the presently claimed ILRAPs would not be associated with IL-2Rα.

In item 9 of the declaration, applicants argue that the experimental result shown in Exhibit 4 indicates that the novel 32-34 kDa ILRAP is expressed on the surface of Kit225 cells, which is lacking on MLA-144 cells, and that in contrast, Colamonici indicates that MLA-144 cells are positive for the expression of the 37 kDa polypeptide (Figure 5), suggesting that they cannot be the same molecules. This has been fully considered, but is not persuasive because the method and experimental conditions used in the prior art reference are completely different from that of the instant application. For instance, Colamonici used immunoprecipitation method, wherein MLA-144 cells were affinity cross-linked with ^{125}I-rIL-2, which is a much sensitive test (radio immunoassay) than fluorescence flow cytometry method used in Exhibit 4. Therefore, a protein may well be detected by a sensitive method but not others for the same purpose. Further, it is noted that Colamonici's MLA-144 cells were stimulated with IL-2, which could have changed the kinetics/abundance of the IL-2R and/or associated molecules, resulting in difference in detection. Such is well established phenomenon. For example, Colamonici teaches that a previously identified protein is present in *stimulated* human and mouse lymphocytes (page 159, the first paragraph of the left column). As another example, Colamonici's p95-110 kDa protein was only detectable in Hut-102 cells under "low affinity conditions" (i.e., cells were stimulated with high concentrations of IL-2 (10 nM)), but not under "medium or high affinity conditions" (lower concentrations of IL-2, 0.5-5 nM) (Figure 3, and page 159, mid of the left column), even with the sensitive radio immunoassay. Therefore, depending upon the method used, cell conditions, and abundance of a protein being produced, the protein may or may not detectable under specific circumstances. It would not be proper to compare results resulted from different experimental methods and under different conditions as they are known for causing potential different results. Thus, no conclusion can be drawn from such comparison, and no factual evidence can be established.

With respect to the interest of the expert in the outcome of the case, Dr. Waldmann is among the inventors of the instant invention.

In summary, the present declaration provides no direct evidence indicating that the claimed polypeptides are distinct from that of the prior art, such as side by side comparison of

the molecules using Hut-102 cells, clearly showing the difference in their MW, because Hut-102 cells are used by both applicants and Colamonici, and hence forms the basis for the prior art rejection. Thus, in the absence of any direct factual support for the expert's opinion, and the presence of opposing evidence (as exemplified above), the declaration insufficient to overcome the prior art rejection.

Rejections under 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 9, 11-15 and 22-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 1, 3, 5, 9, 11-15 and 22-29 are directed to a composition comprising an IL-2R associated polypeptide (ILRAP), and a method for purifying said polypeptide, wherein the ILRAP is associated with IL-2Rα. The specification discloses that an anti-idiotypic antibody directed against murine mAb recognizing human IL-2, 5F7, was used in order to search for additional IL-2R associated proteins, and the present ILRAPs were isolated from IL-2R expressing cells using 5F7 mAb (page 30, lines 20-22, and the paragraph bridging pages 32 and 33), i.e., the mAb 5F7 recognizes neither IL-2Rα, nor any known IL-2R associated polypeptide. Further, nowhere in the specification provides any evidence demonstrating that either ILRAP is associated with IL-2Rα. As opposing evidence, applicants declaration under 37 CFR 1.132 filed on 21 Match 2006 provides experimental data (item 8 and Exhibit 3) indicating that the claimed

ILRAPs do not seem to be associated with IL-2Rα. As indicated by applicants in item 8 of the declaration, the results presented in Exhibit 3 (immunoprecipitation assay) demonstrate the inability of the anti-Tac mAb to remove the claimed ILRAPs from Kit225 cell lysate where both Tac (IL-2Rα) and the claimed polypeptides are expressed. Such is indeed clearly shown in Exhibit 3 as the results in lane 2 (anti-5F7 antibody from non-pre-cleared Kit225 cell lysate) and lane 8 (anti-5F7 antibody from anti-Tac pre-cleared Kit225 cell lysate) appear the same, indicating that the presently claimed ILRAPs are not associated with IL-2Rα in the cell lysate. As such, the claimed polypeptides associated with IL-2Rα, or any IL-2R are not enabled, and undue experimentation would be required to determine such a property of the polypeptides prior to using the claimed invention. In the absence of evidence showing that the claimed ILRAPs are associated with IL-2Rα or any IL-2R, and the presence of the opposing evidence (Exhibit 3), mere mAb 5F7 recognition of the polypeptides is not sufficient to conclude that said polypeptides are associated with IL-2Rα, as the specificity of 5F7 mAb is merely based on its recognition of an antibody to IL-2 (anti-idiotypic), and an epitope recognized by an antibody can be just a few amino acids, which could be shared by other unrelated polypeptides.

Due to the large quantity of experimentation necessary to determine whether the presently claimed polypeptides are associated with IL-2Rα or any IL-2R, the lack of teachings presented in the specification regarding same, the presence of opposing evidence (by applicants declaration) indicting otherwise, the complex nature of the invention, wherein the polypeptides were isolated using an anti-idiotypic antibody (i.e., not known for recognizing the IL-2R associated polypeptide directly), the lack of predictability as it is unclear whether such an antibody would only recognize an IL-2R associated polypeptide, undue experimentation would be required of the skilled artisan to use the claimed invention.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 5, 9, 13-15, 22-25 remain rejected, and the new claims 26-29 are rejected under 35 U.S.C. 102(b) as being anticipated by, or, in the alternative, under 35 U.S.C. 103(a) as obvious over Colamonici et al. (J. Immunol., 1990, 145:155-160), for the reasons of record set forth in the previous Office Action mailed on 6/304, 4/19/05, and 10/18/05.

Applicants argument filed on 21 Match 2006 has been fully considered, but is not deemed persuasive for reasons below.

Based on the Declaration by Dr. Waldmann (the four Exhibits), the applicant argues, at pages 7-9 of the response, that the declaration includes side by side comparative data from SDS-PAGE using MT-1 cells, which distinguish the claimed polypeptides from those of Colamonici's in MW; and provides data demonstrating the presence of the claimed polypeptides in cell lysate from Kit225 cells after pre-cleared with anti-Tac antibody; and that the 32-34 polypeptide is absent on MLA-144 cells as demonstrated by flow cytometry, and Colamonici 37 kDa polypeptide is present on such cells. This argument is not persuasive for the same reasons above addressed under "Declaration".

Conclusion:

No claim is allowed.

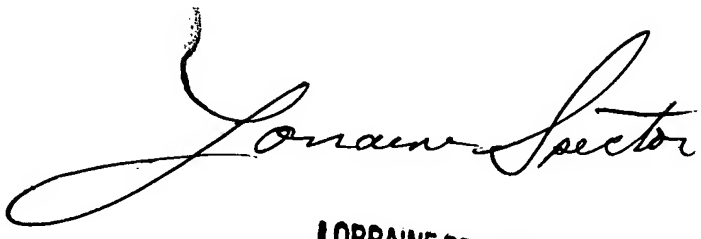
Advisory Information:

Applicant's amendment and experimental results (shown in Exhibits of the declaration) necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



LORRAINE SPECTOR
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AU1646
6/8/06